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A Simple and one-pot synthesis of imintriazole derivatives under Solvent-free conditions

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Abstract: An efficient synthesis of iminetriazole derivatives is described *via* an one-pot reaction between acid chlorides, 3-amino-2-butanone, primary amines and hydrazonoyl chloride under solvent-free conditions at room temperature in good yields. Also, the antimicrobial activity of some synthesized compounds proved by employing the disk diffusion test on Gram-positive and Gram-negative bacteria. This procedure has some benefits such as short reaction time, product with excellent yields, simple catalyst and products separation.

Keywords: Acid chlorides, Hydrazonoyl chloride, 3-amino-2-butanone, Solvent-free, One-pot reaction.

Introduction

MCRs open diverse avenues to create novel concatenations in one pot fashion leading to diverse biologically potent heterocyclic scaffolds [1, 2]. Having a cascade of reactions occurring in one pot is highly beneficial in the context of modern trends for organic synthesis, where sustainability is as relevant as efficiency and selectivity. Multicomponent reactions being atom economic, efficient and extremely convergent in nature offer a number of advantages over stepwise sequential approaches [3–5]. Substituted 1,2,4-triazoles and their derivatives are key skeletons of many biologically active moleculers and important organic compounds, and they exhibit wide applications in pesticides, medicines, functional materials and organocatalysts [5-8]. In addition, a number of natural products contain a 1,2,4- triazole motif [9, 10].

Owing to their important properties and applications, various methods for synthesis of 1,2,4-triazole derivatives have been developed [11, 12]. Azaheterocycles constitute a very important class of compounds.

Currently, biologists, medicinal and food chemist for found out new and economical synthetic antioxidant compounds for protecting of persons against these diseases. Presently, bacteria that are not destroied with drug have generated many problems in the performance of much transferable disease. For this reason, discovering appropriate and new procedures for the dealing with these pathogens are important and recent study have focused on the investigation of the antibacterial effects on the prepared compounds.Thus, the reaction of acid chlorides **1**, 3-amino-2-butanone **2**, methyl amine **3** and hydrazonoyle chloride **4** led to iminetriazole derivatives **5** in excellent yields (Scheme **1**).

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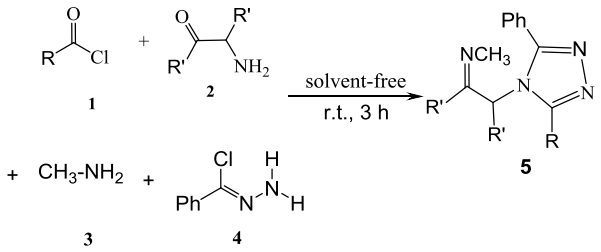
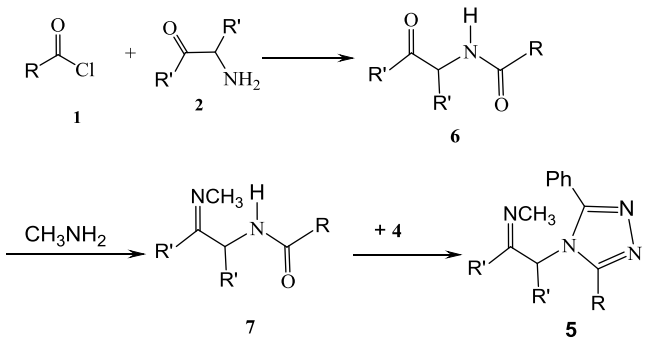


5	R	R'	Yield (%) of 5
a	4-Br-C_6H_4	Ph	90
b	4-Cl-C_6H_4	Ph	85
c	$(CH_3)_3C$	Ph	87
d	4-Me-C_6H_4	CH_3	83
e	$(CH_3)_3C$	CH_3	75

Scheme 1. Synthesis of imine triazole derivatives **5**

Result and discussion

Structures of compounds **5a**–**5e** were assigned by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. The ^{1}H- and ^{13}C-NMR spectroscopic data, as well as IR spectra, are in agreement with the proposed structures. Spectral data for these compounds are given in the experimental section. Mechanistically, the reaction starts with formation of amid derivatives **6**, followed by addition of methyl amine **3** generate the intermediate **7**. Intermediate **7** would be reacted with hydrazonoyl chloride **4** and produced compounds **5** (Scheme 2).



Scheme 2. Proposed mechanism for the preparation of **5**

Evaluation of antibacterial activity of synthesized 1,2,4-triazols

In this research work we investigated the antimicrobial activity of synthesized 1,2,4-triazols in the presence of Gram-positive and Gram-negative bacteria and compared with Streptomycin and Gentamicin as two standard antibacterial drugs. The results of this investigation are displayed in Table 4. The valuation showed that the type of bacteria and concentration of synthesized compounds are important factor on the inhibition zone diameter. As shown in outcomes in Table 4, the antimicrobial ability of 1,2,4-triazols **5a, 5b, 5c, 5d** and **5e** in the presence of two kind of bacteria against two bacteria (Gram positive and negative) have the maximum effect on Escherichia coli due to good diameter of the inhibition zone.

Table 4. The antibacterial activity of some synthesized compounds **5**

Compounds	*Staphylococcus aureus* (+)	*Bacillus cereus* (+)	*Escherichia coli*(-)	*Klebsiella pneumoniae* (-)
5a	**18**	**21**	**22**	**16**
5b	10	8	10	7
5c	6	8	8	6
5d	**20**	**21**	**23**	**18**
5e	**17**	**19**	**22**	**17**
Streptomycin	19	22	23	21
Gentamicin	20	24	22	20

Experimental

Chemicals were purchased from Fluka and used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for the C and H were performed using a Heraeus CHN-O-Rapid analyzer. The results agreed favorably with the calculated values. Mass spectra were recorded on a FINNIGAN-MATT 8430 spectrometer operating at an ionization potential of 70 eV. IR spectra were measured on a Shimadzu IR-460 spectrometer. ^{1}H-, and ^{13}C-NMR spectra were measured with a BRUKER DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz.

General Procedure for the Preparation of 5**:**

A stirred mixture of acid chlorids **1** (0.15 g, 2 mmol) and 3-amino-2-butanone **2** (2 mmol) was stirred under solvent free conditions about 30 min and methyl amine **3** (2 mmol) was added slowly after this time. The hydrazonoyl chloride 4 (2 mmol) was added finally to the mixture and final mixture mixed about 2 h. after completion the reaction, 15 mL of water was poured into the mixture of reaction. The resulting precipitate was separated by filtration and recrystallized by Et_2O (2 mL) to afford the pure title compounds.

2-oxo-1, 2-diphenylethyl 4-bromobenzoate (5a):

Pale yellow powders; m.p. 185-187 ºC; yield: 0.71 g (90%). IR (KBr) (ν_{max}/cm^{-1}): 1708, 1683, 1580, 1398, 1347, 1247, 1099. ^{1}H NMR (500.13 Hz, $CDCl_3$): δ = 7.11 (1 H, s, CH), 7.36-7.43 (5 H, m, 5 CH), 7.53 (1 H, t, ^3J = 7.4 Hz, CH), 7.58 (4 H, m, 4 CH), 8.00 (4 H, t, ^3J = 8.0 Hz, 4 CH) ppm. ^{13}C NMR (125.7 Hz, $CDCl_3$): δ = 78.2 (CH), 128.4 (2 CH), 128.5 (C), 128.7 (CH), 128.8 (2 CH), 128.9 (2 CH), 129.2 (2 CH), 129.4 (2 CH), 131.5 (C), 131.8 (2 CH), 133.5 (CH), 133.6 (C), 134.7 (C), 165.3 (CO_2), 193.4 (CO) ppm. Anal. Calc. for $C_{21}H_{15}BrO_3$ (395.25): C, 63.82; H, 3.83 found: C, 63.78; H, 3.80%.

2-oxo-1, 2-diphenylethyl 4-chlorobenzoate (5b):

White powders; m.p. 174-176 ºC; yield: 0.59 g (85%). IR (KBr) (ν_{max}/cm^{-1}): 1710, 1675, 1512, 1345, 1300, 1295, 1109. ^{1}H NMR (500.13 Hz, $CDCl_3$): δ = 7.22 (1 H, s, CH), 7.42-7.48 (5 H, m, 5 CH), 7.62 (1 H, t, ^3J = 7.4 Hz, CH), 7.68 (4 H, m, 4 CH), 8.10 (4 H, t, ^3J = 8.0 Hz, 4 CH) ppm. ^{13}C NMR (125.7 Hz, $CDCl_3$): δ = 78.5 (CH), 127.9 (2 CH), 128.4 (C), 128.8 (CH), 128.7 (2 CH), 129.4 (2 CH), 129.6 (2 CH), 130.0 (2 CH), 131.2 (C), 132.0 (2 CH), 133.8 (CH), 134.2 (C), 134.9 (C), 166.2 (CO_2), 195.4 (CO) ppm. Anal. Calc. for $C_{21}H_{15}ClO_3$ (350.80): C, 71.90; H, 4.31 found: C, 71.86; H, 4.25%.

2-oxo-1, 2-diphenylethyl pivalate (5c):

White powders; m.p. 145-147 ºC; yield: 0.52 g (87%). IR (KBr) (ν_{max}/cm^{-1}): 1725, 1645, 1557, 1445, 1227, 1112. ^{1}H NMR (500.13 Hz, $CDCl_3$): δ = 1.23 (9 H, s, 3 Me), 7.27 (1 H, s, CH), 7.43 (3 H, m, 2 CH), 7.50 (1 H, m, CH), 7.58 (2 H, d, ^3J = 7.4 Hz, 2 CH), 7.95 (2 H, d, ^3J = 7.8 Hz, 2 CH), 8.14 (2 H, d, ^3J = 7.8 Hz, 2 CH) ppm. ^{13}C NMR (125.7 Hz, $CDCl_3$): δ = 27.5 (3 Me), 37.5 (C), 78.2 (CH), 123.4 (C), 124.7 (2CH), 127.6 (CH), 128.4 (2 CH), 128.6 (2 CH), 129.1 (2 CH), 131.7 (CH), 134.7 (C), 168.2 (CO_2), 197.5 (CO) ppm. Anal. Calc. for $C_{19}H_{20}O_3$ (296.36): C, 77.00; H, 6.80 found: C, 76.95; H, 6.78%.

1-methyl-2-oxopropyl 4-methylbenzoate (5d):

Yellow powders; m.p. 168-170 ºC; yield: 0.34 g (83%). IR (KBr) (ν_{max}/cm^{-1}): 1734, 1625, 1498, 1427, 1200, 1015. ^{1}H NMR (500.13 Hz, $CDCl_3$): δ = 1.28 (6 H, d, ^3J = 7.5 Hz, 2 Me), 2.15 (Me), 2.36 (Me), 5.42 (1 H, q, ^3J = 7.5 Hz, CH), 7.58 (2 H, d, ^3J = 7.5 Hz, 2 CH), 7.75 (2 H, d, ^3J = 7.5 Hz, 2 CH) ppm. ^{13}C NMR (125.7 Hz, $CDCl_3$): δ = 16.5 (Me), 21.7 (Me), 24.3 (Me), 75.7 (CH), 127.6 (C), 127.8 (2CH), 128.4 (2 CH), 138.7 (C), 168.8 (CO_2), 200.6 (CO) ppm. Anal. Calc. for $C_{12}H_{14}O_3$ (206.24): C, 69.89; H, 6.84 found: C, 69.85; H, 6.79%.

1-methyl-2-oxopropyl pivalate (5e):

Yellow oil; yield: 0.26 g (75%). IR (KBr) (ν_{max}/cm^{-1}): 1767, 1638, 1354, 1154, 1028. ^{1}H NMR (500.13 Hz, $CDCl_3$): δ = 1.14 (9 H, s, 3 Me), 1.25 (3 H, d, ^3J = 7.3 Hz, Me), 2.24 (Me), 5.32 (1 H, q, ^3J = 7.3 Hz, CH) ppm. ^{13}C NMR (125.7 Hz, $CDCl_3$): δ = 17.2 (Me), 24.8 (Me), 27.6 (3 Me), 41.5 (C), 76.8 (CH), 178.8 (CO_2), 204.2 (CO) ppm. Anal. Calc. for $C_9H_{16}O_3$ (172.22): C, 62.77; H, 9.36 found: C, 62.68; H, 9.26%.

Study of prepared 1,2,4-triazols antibacterial ability:

Gram-positive and Gram-negative bacteria were utilized for investigation of antibacterial effect of synthesized 1,2,4-triazols against two standards such as Streptomycin and Gentamicin with a concentration 40 μg/mL by employing the disk diffusion procedure. Two types of bacteria that are used in this experiment were produced from the Persian type culture collection (PTCC), Tehran, Iran. The bacteria were cultured for 16 to 24 h at 37°C for preparing the turbidity equivalent bacteria to McFarland Standard No. 0.5. The bacterial suspension was produced according to the turbidity of the 0.5 McFarland (About 1.5 × 108 CFU/mL) standards and cultured with a sterile swab on Mueller Hinton agar. For valuation of their antibacterial activity of 1,2,4-triazols with concentration of 25 µg/ml were poured on sterile blank disks. The plates were incubated in an incubator at 37 °C for 24 h. The inhibition zone diameter was measured and compared to with the standard.

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